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(54) **Title:** NOVEL ORTHOGONALLY PROTECTED AMINO ACID CHELATORS FOR BIOMEDICAL APPLICATIONS

(57) **Abstract:** Polyazacarboxylates and their peptide conjugates which are useful for imaging, diagnosis and therapy are disclosed. Particularly, this invention relates to compositions of two or more peptides that are conjugated to a molecule of polyazacarboxylate ligand. The compounds of this invention are in the general formula (1): $R_1NHC(O)$-LS-$C(O)NHR_2$, wherein R_1 and R_2 are peptides with the same or different receptor affinities and LS is a cyclic or linear polyazacarboxylates. The are useful for therapeutic and contrast agents in biomedical applications.

NOVEL ORTHOGONALLY PROTECTED AMINO ACID CHELATORS FOR BIOMEDICAL APPLICATIONS

FIELD OF INVENTION

This invention relates to polyazacarboxylates and their peptide conjugates which are useful for imaging, diagnosis and therapy. Particularly, this invention relates to compositions of two or more peptides that are conjugated to a molecule of polyazacarboxylate ligand. The compounds of this invention have the general formula:

$$R_1NHC(O)\text{-}LS\text{-}C(O)NHR_2$$

Formula 1

wherein R_1 and R_2 are peptides with the same or different receptor affinities and LS is a cyclic or linear polyazacarboxylates. They are useful for therapeutic and contrast agents in biomedical applications.

BACKGROUND OF THE INVENTION

The surge of interest in the use of peptides and other biocompatible markers to target tumors have led to the identification of a host of receptors that are over-expressed by certain tumors (J. C. Reubi, Neuropeptide receptors in health and disease: the molecular basis for *in vivo* imaging. *Journal of Nuclear Medicine*, 1995, 36, 1825-1835; A. J. Fischman, J. W. Babich, and H. W. Strauss, A ticket to ride: Peptide radiopharmaceuticals. *Journal of Nuclear Medicine*, 1993, 34, 2253-2263). The tumors can then be visualized and destroyed by agents that target the receptors which are over-expressed in the given tumor (J. E. Bugaj, J. L. Erion, M. A. Schmidt, R. R. Wilhelm, S. I. Achilefu, A. Srinivasan, Biodistribution and Radiotherapy Studies Using Samarium-153 and Lutetium-177 DTPA Conjugates of Y^3- Octreotate. *Journal. Nuclear Medicine.*, 1999, 40(5), 223P). This site-specific delivery of contrast agents enables the differentiation of normal from diseased tissues and also preserves normal tissues from lethal therapeutic drugs.

A current method for tumor imaging involves the conjugation of radioactive metal chelates to antibodies or peptides that target the abundant receptors on a given tumor (R. Albert, E. P. Krenning, S. W. J. Lamberts, and J. Pless, Use of certain somatostatin peptides for the in vivo imaging of somatostatin receptor-positive tumors and metastasis. US 5,753,627). Careful

selection of metals and peptides determines the imaging modality and therapeutic potential of the chelate-peptide conjugate. For example, gadolinium chelates are used for magnetic resonance imaging (A. D. Nunn, K. E. Linder, and M. F. Tweendle, Can receptors be imaged with MRI agent? *The Quarterly Journal of Nuclear Medicine*, 1997, 41(2), 155-162), radioactive metals are used for scintigraphy (e.g. technetium-99, indium-111, see A. Srinivasan, M. M Dyszlewski, J. E. Bugaj, and J. L. Erion, Radiolabeled peptide compositions for site-specific targeting. US 5,830,431), or therapy (e.g. lutetium, yttrium see J. E. Bugaj, J. L. Erion, M. A. Schmidt, R. R. Wilhelm, S.I. Achilefu, A. Srinivasan, Biodistribution and Radiotherapy Studies Using Samarium-153 and Lutetium-177 DTPA Conjugates of Y^3- Octreotate. *Journal. Nuclear Medicine.*, 1999, 40(5), 223P), and bioactive peptides (S. W. J. Lamberts, E. P. Krenning, and J. C. Reubi, The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocrine Reviews*, 1991, 12(4), 450-478) can function as both delivery and therapeutic agents. In general, the metal chelates are attached to free amino groups of antibodies and peptides (R. Albert, E. P. Krenning, S. W. J. Lamberts, and J. Pless, Use of certain somatostatin peptides for the in vivo imaging of somatostatin receptor-positive tumors and metastasis. US 5,753,627). However, results from several investigations indicate that a single tumor line may over-express more than one class receptors (for example, breast tumor may overexpress either estrogen, somatostatin or bombesin receptors) and the receptor density may vary from one patient to another (S. W. J. Lamberts, E. P. Krenning, and J. C. Reubi, The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocrine Reviews*, 1991, 12(4), 450-478; S. R. Preston, G. V. Miller, and J. M. Primrose, Bombesin-like peptides and cancer. *Critical Reviews in Oncology/Hematology*, 1996, 23, 225-238). Hence, the conventional method of attaching a metal chelate to a tumor targeting group could lead to many false negatives which could lead to deaths. A logical approach to solving this problem involves the administration of a cocktail of chelate-metal conjugates to the patient. While this method may improve diagnosis, it will require the synthesis and development of several peptide-chelate conjugates which will drastically increase the cost of health care. Also, dose formulation would become a major problem because of possible incompatibilities of such mixtures. Further, isolation of the cause of any observed side-effect would become an arduous task for the physician. Finally, a minimum radiation dose is usually required for the detection of radioactive markers in tissues. Each

component of the cocktail must, therefore, contain this threshold of radioactivity. Hence, the net radiation dose administered to the patient would be unacceptable.

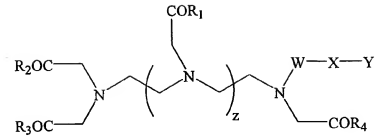
A better approach would be to incorporate two or more peptides that have high affinity for the most common receptors in a given diseased state. This would require a linker to combine the peptides into one molecule. For scintigraphic applications, a ligand is required to chelate the metal radionuclide of interest. Dunn and Srinivasan described a method for incorporating ligand precursors into peptides (US Patent 5,798,444 and US Patent 5,734,011). However, their method only introduces a ligand precursor and requires elaborate chemistries on solid support to complete the ligand synthesis. The teachings of Dunn and Srinivasan are limited in scope because of the *in vivo* instability of the EDTA metal chelates and the series of stereochemical controls required to synthesize the ligand precursors are cumbersome. Further, the teachings of Dunn and Srinivasan relate to the incorporation of ligands at any chosen position on the same peptide sequence.

There remains a need to develop a dynamic method for the incorporation of two or more bioactive peptides or proteins to a chelate which can be used to target various over-expressed receptors on tumors. This would immensely decrease the number of false negatives that limit the use of current radiolabeled peptides and proteins. Further, incorporation of such peptides to the ligand should not result in the loss of *in vivo* stability of the chelate. Also, minimization of patient exposure to radiation is highly desirable. Finally, a method for the automated synthesis of such compounds on solid support, which is also amenable to combinatorial synthesis, would be desirable. Such compositions and methods are disclosed in this invention.

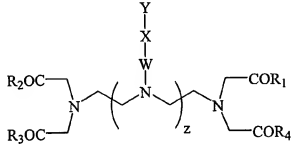
The publications and other materials used herein to support the background of the invention or provide additional details respecting the practice, are incorporated by reference.

SUMMARY OF THE INVENTION

The present invention relates particularly to the novel composition comprising polyazacarboxylates of the formula 1 or 1a:



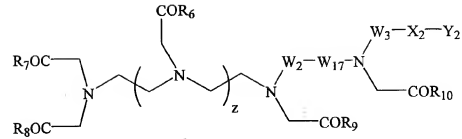
1



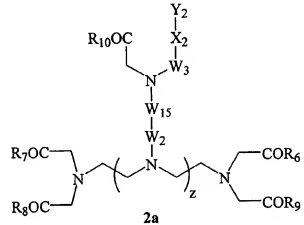
1a

wherein R_1 to R_4 may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, or X-Y; W is selected from the group consisting of alkyl, aryl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, polyhydroxyalkyl, or polyhydroxyaryl; X is selected from the group consisting of -NH, -CONH-, $-CH_2NH$-, $-CH_2NR_5$-, -COO-, -O-, -C(O)-, -S-, -NHCO-, or -NHC(S)-; Y is selected from alkyl amines, aryl amines, polyhydroxyalkyl amines, polyalkoxyalkyl amines or bioactive molecules, b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, or aryl; R_5 is as defined for R_1; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and z varies from 1-10, preferably 1-3.

The present invention also relates to novel compositions comprising a polyazacarboxylate of the formula 2 or 2a:



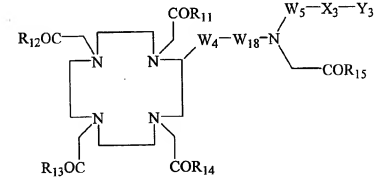
2



2a

wherein R_6 to R_{10} are defined in the same manner as R_1 to R_4; X_2 and Y_2 are defined in the same manner as X and Y respectively; W_2 and W_3 are as defined for W; W_{17} is C=O, CH_2, or OC_2H_4; and z varies from 1-10, preferably 1-3.

The present invention also relates to novel compositions comprising a polyazacarboxylate of the formula 3:

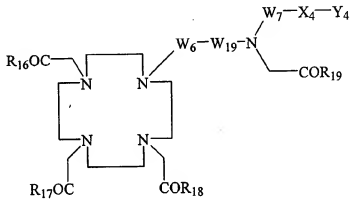


3

wherein R_{11} to R_{15} are defined in the same manner as R_1 to R_4; X_3 and Y_3 are defined in the same manner as X and Y, respectively; W_4 and W_5 are as defined for W; and W_{18} is as defined for W_{15}.

The present invention also relates to novel compositions comprising a polyazacarboxylate of the formula 4:

The present invention also relates to a method of preparing a carboxyl-terminal chelator composition comprising polyazacarboxylates of the formula 4:



4

wherein R_{16} to R_{19} are defined in the same manner as R_1 to R_4; X_4 and Y_4 are defined in the same manner as X and Y, respectively; W_6 and W_7 are as defined for W; and W_{19} is C=O, CH_2 or OC_2H_4.

This invention is also related to the methods of preparing any of the composition of formulas 1 to 4.

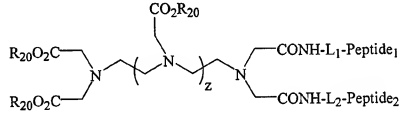
DETAILED DESCRIPTION OF THE INVENTION

In this disclosure, numerical values and ranges are not critical unless otherwise stated. That is, the numerical values and ranges may be read as if they were prefaced with the word "about" or "substantially."

The novel compositions of the present invention comprising polyazacarboxylates of formulas 1 to 4 offer significant advantages over those currently described in the art. As illustrated below, the chelators are designed to either mimic the reactivity of amino acids or they possess at least one free dicarboxylic acid group on the same molecule. This ensures the rapid attachment of two or more different bioactive peptides on the same molecule. Depending on the

metal chelate desired, each chelating group is designed to assure in vivo stability on conjugating two or more peptides. The synthetic procedures described in this invention are amenable to either solid or solution phase synthesis and are compatible with combinatorial synthesis of an array of products. Further, the compounds of this invention are compatible with automated organic synthesis procedures. These compositions are particularly useful when one peptide requires a free amino terminus and the other peptide requires a free carboxyl terminus for their bioactivity.

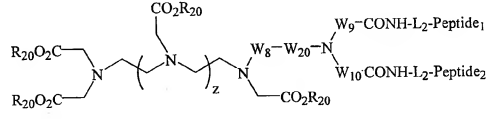
In a preferred embodiment, the polyazacarboxylic acid bis-peptide conjugates according to the present invention have the general formula 5:



5

wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of $-(CH_2)_t-NHC(O)-$ or $-CH_2-(CH_2-O-CH_2)_u-NHC(O)-$; t varies from 1 to 10; u varies from 1 to 50; and z varies from 1 to 10, preferably from 1 to 3. $Peptide_1$ and $Peptide_2$ have affinities toward the same or different tumor receptors.

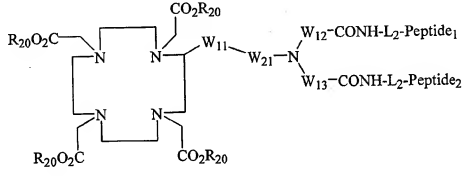
In another preferred embodiment, the polyazacarboxylic acid bis-peptide conjugates according to the present invention have the general formula 6:



6

wherein R_{20}, L_1, L_2, $Peptide_1$, and $Peptide_2$ are as defined in formula 5; W_8 to W_{10} may be the same or different and may be selected from the group consisting of $(CH_2)_h$ or $(CH_2CH_2O)_j$ wherein h varies from 1 to 10 and j varies from 1 to 50; W_{20} is defined as W_{17}; and z varies from 1 to 10, preferably from 1 to 3.

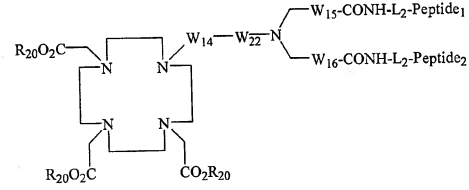
In yet another preferred embodiment, the polyazacarboxylic acid bis-peptide conjugates according to the present invention have the general formula 7:



7

wherein R_{20}, L_1, L_2, $Peptide_1$, and $Peptide_2$ are as defined in formula 5; W_{11} to W_{13} are as defined for W_8 to W_{10}; and W_{21} is as defined for W_{17}.

In another preferred embodiment, the polyazacarboxylic acid bis-peptide conjugates according to the present invention have the general formula 8:



8

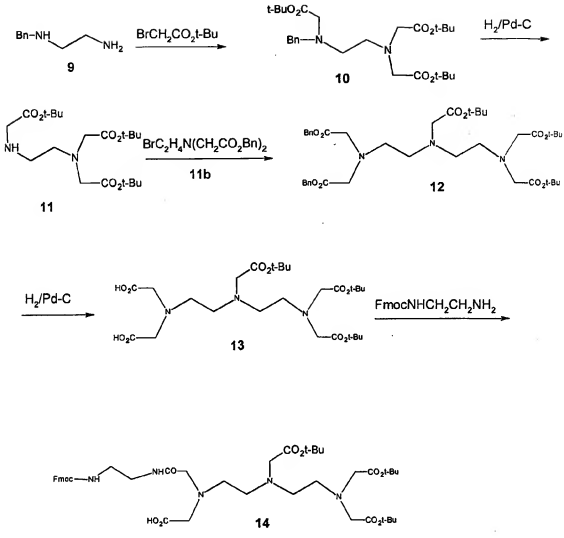
wherein R_{20}, L_1, L_2, $Peptide_1$, and $Peptide_2$ are as defined in formula 5; W_{14} to W_{16} are as defined for W_8 to W_{10}; and W_{22} is as defined for W_{17}.

The invention also relates to the location of the multi-bioactive peptides on any R_{20} as amide derivatives.

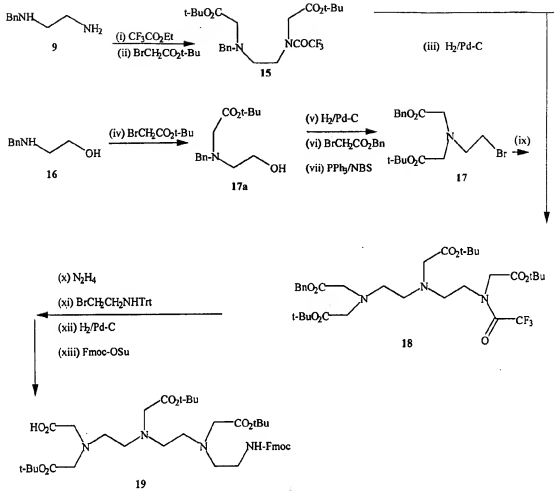
The invention includes methods for synthesizing intermediates and compounds of the formulas 1 to 4 as illustrated in schemes 1 to 14.

The invention also includes the use of the formulations disclosed herein for the synthesis of a combinatorial library of compounds.

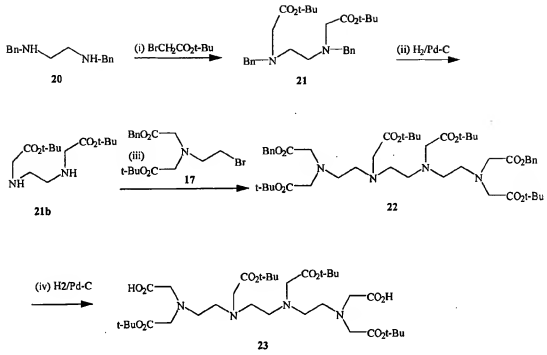
Scheme 1


Bn–NH
NH2
BrCH2CO2t-Bu
t-BuO2C
Bn–N
CO2t-Bu
N
CO2t-Bu
H2/Pd-C
9
10
NH
BrC2H4N(CH2CO2Bn)2
11b
BnO2C
11
12
HO2C
FmocNHCH2CH2NH2
13
Fmoc—NH
NHCO
14

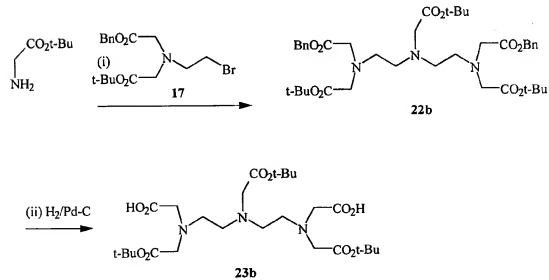
Scheme 2


BnNH
NH2
9
(i) CF3CO2Et
(ii) BrCH2CO2t-Bu
t-BuO2C
CO2t-Bu
Bn-N
NCOCF3
15
(iii) H2/Pd-C
BnNH
OH
16
(iv) BrCH2CO2t-Bu
CO2t-Bu
Bn-N
OH
17a
(v) H2/Pd-C
(vi) BrCH2CO2Bn
(vii) PPh3/NBS
BnO2C
t-BuO2C
Br
17
(ix)
CO2t-Bu
BnO2C
t-BuO2C
CO2tBu
CF3
O
18
(x) N2H4
(xi) BrCH2CH2NHTrt
(xii) H2/Pd-C
(xiii) Fmoc-OSu
CO2t-Bu
HO2C
t-BuO2C
CO2tBu
NH-Fmoc
19

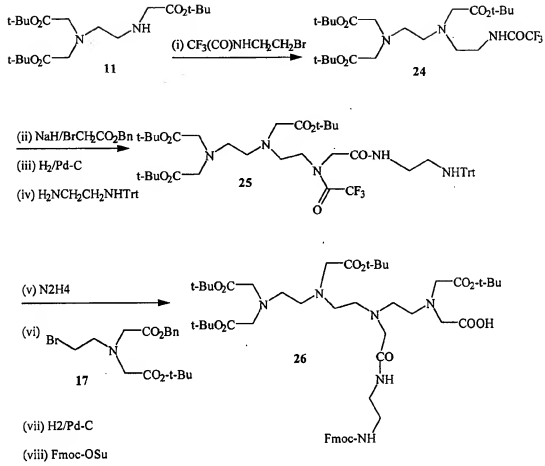
Scheme 3



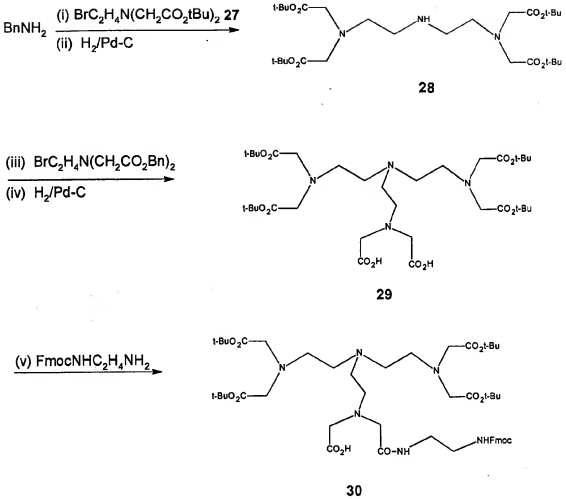
Scheme 3b



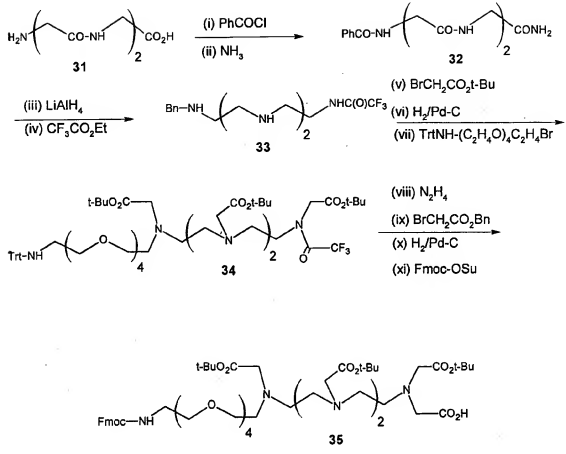
Scheme 4


t-BuO2C
CO2t-Bu
NH
N
t-BuO2C
11
(i) CF3(CO)NHCH2CH2Br
t-BuO2C
CO2t-Bu
NHCOCF3
N
t-BuO2C
24
(ii) NaH/BrCH2CO2Bn
(iii) H2/Pd-C
(iv) H2NCH2CH2NHTrt
t-BuO2C
CO2t-Bu
CO-NH
NHTrt
CF3
O
25
(v) N2H4
(vi)
Br
CO2Bn
CO2-t-Bu
17
CO2-t-Bu
CO2-t-Bu
COOH
CO
NH
Fmoc-NH
26
(vii) H2/Pd-C
(viii) Fmoc-OSu

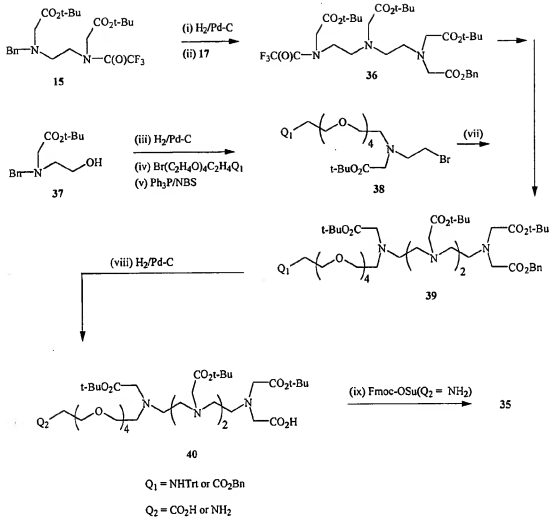
Scheme 5


BnNH2
(i) BrC2H4N(CH2CO2tBu)2 27
(ii) H2/Pd-C
t-BuO2C
CO2t-Bu
NH
N
28
(iii) BrC2H4N(CH2CO2Bn)2
(iv) H2/Pd-C
CO2H
29
(v) FmocNHC2H4NH2
CO-NH
NHFmoc
30

Scheme 6


(i) PhCOCl
(ii) NH3
(iii) LiAlH4
(iv) CF3CO2Et
(v) BrCH2CO2t-Bu
(vi) H2/Pd-C
(vii) TrtNH-(C2H4O)4C2H4Br
(viii) N2H4
(ix) BrCH2CO2Bn
(x) H2/Pd-C
(xi) Fmoc-OSu
31
32
33
34
35

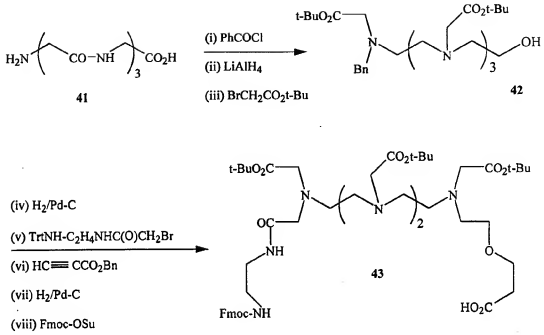
Scheme 7



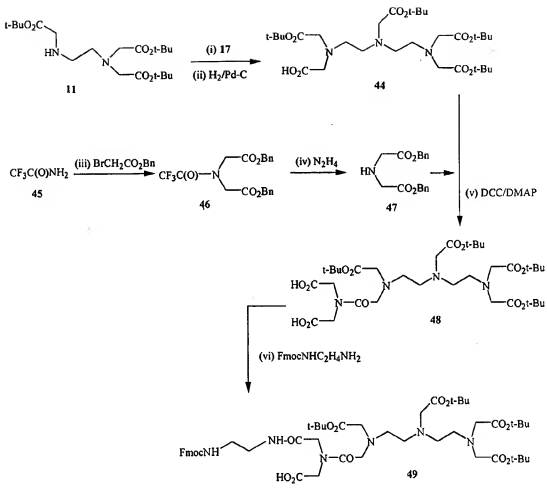
Q_1 = NHTrt or CO_2Bn

Q_2 = CO_2H or NH_2

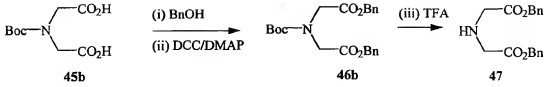
Scheme 8


H2N
CO–NH
CO2H
3
41
(i) PhCOCl
(ii) LiAlH4
(iii) BrCH2CO2t-Bu
t-BuO2C
CO2t-Bu
N
Bn
N
OH
3
42
(iv) H2/Pd-C
(v) TrtNH-C2H4NHC(O)CH2Br
(vi) HC≡CCO2Bn
(vii) H2/Pd-C
(viii) Fmoc-OSu
t-BuO2C
CO2t-Bu
CO2t-Bu
N
N
N
OC
NH
2
O
43
Fmoc-NH
HO2C

Scheme 9

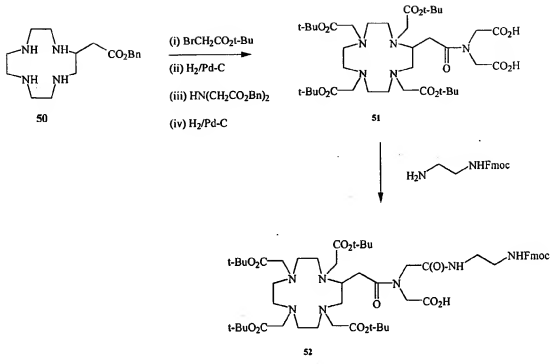

t-BuO2C
HN
CO2t-Bu
CO2t-Bu
11
(i) 17
(ii) H2/Pd-C
HO2C
44
CF3C(O)NH2
45
(iii) BrCH2CO2Bn
CF3C(O)
CO2Bn
46
(iv) N2H4
47
(v) DCC/DMAP
48
(vi) FmocNHC2H4NH2
FmocNH
NH-OC
CO
49

Scheme 9b



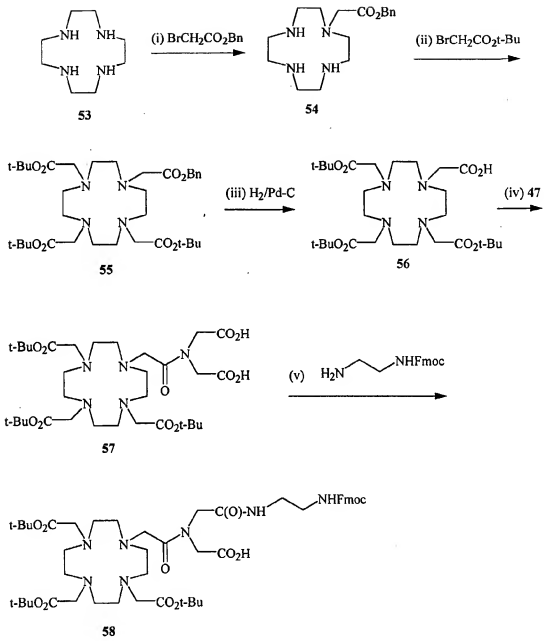
45b 46b 47

Scheme 10

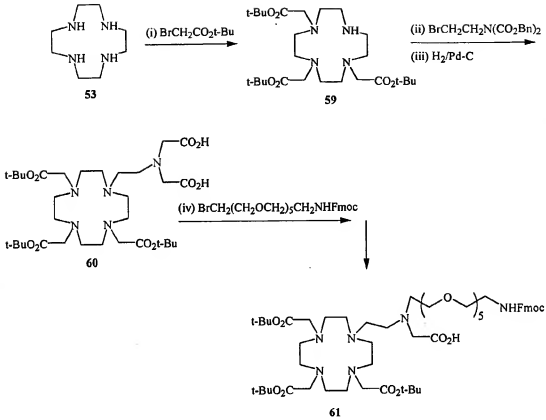


50 51 52

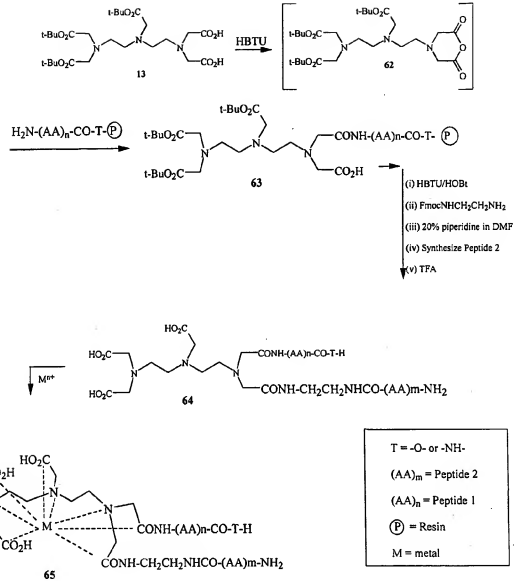
Scheme 11


(i) BrCH2CO2Bn
(ii) BrCH2CO2t-Bu
(iii) H2/Pd-C
(iv) 47
(v)
NHFmoc
C(O)-NH
53
54
55
56
57
58

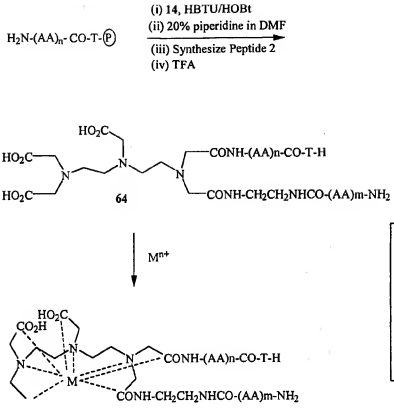
Scheme 12


(i) BrCH2CO2t-Bu
(ii) BrCH2CH2N(CO2Bn)2
(iii) H2/Pd-C
(iv) BrCH2(CH2OCH2)2CH2NHFmoc
53
59
60
61

Scheme 13


t-BuO2C
CO2H
HBTU
13
62
H2N-(AA)n-CO-T-P
CONH-(AA)n-CO-T-P
63
(i) HBTU/HOBt
(ii) FmocNHCH2CH2NH2
(iii) 20% piperidine in DMF
(iv) Synthesize Peptide 2
(v) TFA
HO2C
CONH-(AA)n-CO-T-H
Mn+
CONH-CH2CH2NHCO-(AA)m-NH2
64
M
65
T = -O- or -NH-
(AA)m = Peptide 2
(AA)n = Peptide 1
P = Resin
M = metal

Scheme 14


H2N-(AA)n-CO-T-(P)
(i) 14, HBTU/HOBt
(ii) 20% piperidine in DMF
(iii) Synthesize Peptide 2
(iv) TFA
HO2C
CONH-(AA)n-CO-T-H
CONH-CH2CH2NHCO-(AA)m-NH2
64
Mn+
CO2H
65
T = -O- or -NH-
(AA)m = Peptide 2
(AA)n = Peptide 1
(P) = Resin
M = Metal

Compounds of Schemes 1, 4, 5 and 9 to 12 are particularly useful for the synthesis of bis-peptides that have the same receptor affinity where such constructs serve to augment tumor receptor binding and enhance specificity. They are also useful for the synthesis of peptides with affinities towards different receptors but do not cause detrimental intramolecular interactions between each peptide. Compounds of Schemes 2, 3 and 6 to 8 are particularly useful for the synthesis of bis-peptides with affinities for different tumor receptors and minimize intramolecular interaction.

The compositions of the invention can be formulated into diagnostic compositions for enteral or parenteral administration. These compositions contain an effective amount of the dye along with conventional pharmaceutical carriers and excipients appropriate for the type of administration contemplated. For example, parenteral formulations advantageously contain a sterile aqueous solution or suspension of dye according to this invention. Parenteral compositions may be injected directly or mixed with a large volume parenteral composition for systemic administration. Such solutions also may contain pharmaceutically acceptable buffers and, optionally, electrolytes such as sodium chloride.

Formulations for enteral administration may vary widely, as is well known in the art. In general, such formulations are liquids which include an effective amount of the dye in aqueous solution or suspension. Such enteral compositions may optionally include buffers, surfactants, thixotropic agents, and the like. Compositions for oral administration may also contain flavoring agents and other ingredients for enhancing their organoleptic qualities.

The diagnostic compositions are administered in doses effective to achieve the desired enhancement. Such doses may vary widely, depending upon the particular dye employed, the organs or tissues which are the subject of the imaging procedure, the imaging equipment being used, and the like.

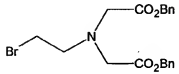
The diagnostic compositions of the invention are used in the conventional manner. The compositions may be administered to a patient, typically a warm-blooded animal, either systemically or locally to the organ or tissue to be imaged, and the patient is then subjected to the imaging procedure.

A combination of the above represents an important approach to the synthesis and use of novel polyazacarboxylates as chelators and linkers in the preparation of multi-bioactive molecules. The present invention is further detailed in the following Examples, which are

offered by way of illustration and are not intended to limit the scope of the invention in any manner.

EXAMPLE 1

Synthesis of



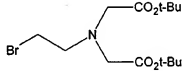
[Scheme 1, **11b**] A solution of 50 ml of dimethylformamide and benzyl bromoacetate (16.0 g, 70 mmol) was stirred in a 100 ml three-neck flask. Solid potassium bicarbonate (7.8 g, 78 mmol) was added. The flask was purged with argon and cooled to 0°C with an ice bath. To the stirring mixture was added dropwise a solution of ethanolamine (1.9 g, 31 mmol) and 4 ml of dimethylformamide over 5 minutes. After the addition was complete the mixture was stirred for 1 hour at 0°C. The ice bath was removed and the mixture stirred at room temperature overnight. The reaction mixture was partitioned between 100 ml of methylene chloride and 100 ml of saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was again washed with 100 ml of saturated sodium bicarbonate solution. The combined aqueous layers were extracted twice with 25 ml of methylene chloride. The combined methylene chloride layers were washed with 100 ml of brine, and dried over magnesium sulfate. The methylene chloride was removed with aspirator vacuum at ca. 35°C, and the remaining dimethylformamide was removed with vacuum at about 45°C. The crude material was left on a vacuum line overnight at room temperature.

The crude material from above was dissolved in 100 ml of methylene chloride at room temperature. Triphenylphosphine (8.91 g, 34 mmol) was added and dissolved with stirring. An argon purge was started and the mixture cooled to 0°C with an ice bath. The N-bromosuccinimide (6.05 g, 34 mmol) was added portionwise over 2 minutes. The mixture was stirred for 1.5 hours at 0°C. The methylene chloride was removed with vacuum and gave a purple oil. This oil was triturated with 200 ml of ether with constant manual stirring. During this time the oil became very thick. The ether solution was decanted and the oil was triturated with 100 ml of ether. The ether solution was decanted and the oil was again triturated with a 100 ml

portion of ether. The ether was decanted and the combined ether solutions allowed to stand for about 2 hours to allow the triphenylphosphine oxide to crystallize. The ether solution was decanted from the crystals and the solid washed with 100 ml of ether. The volume of the combined ether abstracts was reduced with vacuum until a volume of about 25 ml was obtained. This was allowed to stand overnight at 0°C. Ether (10 ml) was added to the cold mixture which was mixed to suspend the solid. The mixture was percolated through a column of 45 g of silica gel and eluted with ether, and 75 ml fractions were collected. The fractions that contained product by TLC were pooled and the ether removed with vacuum. This gave 10.1 g of crude product. The material was flash chromatographed on silica gel with hexane, changing to 9:1 hexane:ether. The product-containing fractions were pooled and the solvents removed with vacuum. This gave 7.4 g (57% yield) of pure product.

EXAMPLE 2

Synthesis of



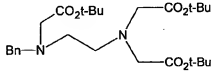
[Scheme 5, **27**] A solution of 370 ml of dimethylformamide and t-butyl bromoacetate (100 g, 510 mmol) was stirred in a 1000 ml three-neck flask. Solid potassium bicarbonate (57 g, 570 mmol) was added. The flask was purged with argon and cooled to 0°C with an ice bath. To the stirring mixture was added dropwise a solution of ethanolamine (13.9 g, 230 mmol) in 30 ml of dimethylformamide over 15 minutes. After the addition was complete the mixture was stirred for 1 hour at 0°C. The ice bath was removed and the mixture stirred at room temperature for 12 hours. The reaction mixture was partitioned between 700 ml of methylene chloride and 700 ml of saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was again washed with 700 ml of saturated sodium bicarbonate solution. The combined aqueous layers were extracted twice with 200 ml of methylene chloride. The combined methylene chloride layers were washed with 500 ml of brine, and dried over magnesium sulfate. The methylene chloride was removed with aspirator vacuum at ca. 35°C, and

the remaining dimethylformamide was removed with vacuum at about 45°C. The crude material was left on a vacuum line overnight at room temperature.

The crude material from above was dissolved in 600 ml of methylene chloride at room temperature. Triphenylphosphine (65.8 g, 250 mmol) was added and dissolved with stirring. An argon purge was started and the mixture cooled to 0°C with an ice bath. The N-bromosuccinimide (44.7 g, 250 mmol) was added portion-wise over 5 minutes. The mixture was stirred for 1.5 hours at 0°C. The methylene chloride was removed with vacuum and gave a purple oil. This oil was triturated with 500 ml of ether with constant manual stirring. During this time the oil became very thick. The ether solution was decanted and the oil was triturated with 500 ml of ether. The ether solution was decanted and the oil was again triturated with a 500 ml portion of ether. The ether was decanted and the combined ether solutions allowed to stand for about 2 hours to allow the triphenylphosphine oxide to crystallize. The ether solution was decanted from the crystals and the solid washed with 500 ml of ether. The volume of the combined ether abstracts was reduced with vacuum until a volume of about 80 ml was obtained. This was allowed to stand over night at 0°C. Ether (100 ml) was added to the cold mixture which was mixed to suspend the solid. The mixture was filtered and washed ten times with 4 ml of ether. The solution was percolated through a column of 500 g of silica gel and eluted with 500 ml portions of ether, 500 ml fractions were collected. The fractions that contained product by TLC were pooled and the ether removed en vacuo. This gave 68.6 g of crude product. The material was flash chromatographed on silica gel with hexane, changing to 9:1 hexane:ether. The product-containing fractions were pooled and the solvents removed en vacuo. This gave 54 g (67% yield) of pure product.

EXAMPLE 3

Synthesis of

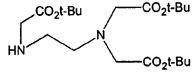


[Scheme 1, **10**] N-Benzylethylenediamine (5g, 33.28 mmol) and potassium bicarbonate (19.3 g, 139.7 mmol) were added to 200 ml of anhydrous acetonitrile and stirred vigorously

under argon. t-Butyl bromoacetate (22.7 g, 116.5 mmol) was diluted in 30 ml of anhydrous acetonitrile and the solution was added dropwise to the reaction mixture over 90 minutes. The progress of the reaction was monitored by TLC and was essentially complete in about 4 hours but was stirred at room temperature for about 12 hours in order to assure complete alkylation of the amine. The insoluble residue was filtered and washed with acetonitrile. The filtrate was evaporated to give 20 g of a yellow liquid. Hexane (100 ml) was added to the crude mixture and stirred vigorously until white precipitate formed. The precipitate was filtered and the filtrate was evaporated to give a yellow liquid. The pure compound was obtained by washing the crude product over dry flash chromatographic column and the desired compound was eluted with 10% diethyl ether in hexane (12.5 g, 80% yield).

EXAMPLE 4

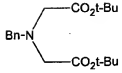
Synthesis of



[Scheme 1, **11**] N-benzyl-N,N'N'-tris(t-butyloxycarbonylmethyl) ethylenediamine (**10**; 6 g, 12 mmol) was added to a heterogeneous mixture of 10% palladium on carbon (6 g, 1 weight equivalent) in 100 ml of methanol. Anhydrous ammonium formate (3.8 g, 60.26 mmol) was added to the reaction mixture in one bulk. The mixture was stirred at room temperature for 2 hours. The mixture was filtered over celite and the residue was washed with chloroform. The filtrate was evaporated until white precipitates began to form. The residue was triturated in chloroform and the insoluble formate was filtered. Evaporation of the filtrate gave a pale yellow liquid (4.6 g, 96% yield) which was identified as the pure compound by NMR analysis.

EXAMPLE 5

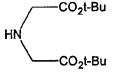
Synthesis of



A mixture of benzylamine (10 g, 0.93 mol) and $KHCO_3$ (35 g, 3.5 mol) in acetonitrile (100 mL) was cooled to 0°C and t-butyl bromoacetate (39 g, 2.0 mol) was added dropwise. After complete addition of the bromide, the mixture was allowed to reach room temperature and stirred for 16 hours. It was filtered and the residue was washed with acetonitrile. The solvent was evaporated from the filtrate. The crude product was taken up in 100 ml of dichloromethane and washed with water (3 X 75 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated. Further purification was performed by flash chromatography using 10% ether in hexane. This gave 26.6 g (85%) of the pure compound.

EXAMPLE 6

Synthesis of



Two methods were used for the debenzylation of N,N-bis(t-butyloxycarbonylmethyl) benzylamine (from Example 5).

In Method A, a mixture of N,N-bis(t-butyloxycarbonylmethyl) benzylamine (5 g, 14.8 mmol), ammonium formate (2.4 g) and 10% Pd-C (1 g) in methanol (50 mL) was refluxed for 30 minutes. Upon cooling to ambient temperature, the catalyst was filtered over celite and the cake was washed with methanol. The solvent was evaporated and the residue extracted with chloroform. Filtration of the extract and evaporation of the solvent gave the pure secondary amine (3.4 g, 94%) as an oil.

In Method B, a mixture of N,N-bis(t-butyloxycarbonylmethyl) benzylamine (6 g, 19.5 mmol) and 10% Pd-C (0.6 g) in methanol (60 mL) was hydrogenolyzed at 45 psi for 2 hours.

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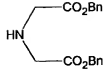
EXAMPLE 8B

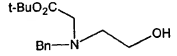
Synthesis of



[Scheme 9b, compound **47**] Benzyl alcohol (5.1 g, 47.17 mmol) was added to a suspension of t-butoxycarbonyl (Boc) imminodiacetic acid (**45b**, 5 g, 21.44 mmol) in anhydrous dichloromethane (DCM). Dimethylformamide (DMF) was added dropwise until a clear solution was obtained. The solution was cooled to 0°C and a mixture of dicyclohexylcarbodiimide (DCC, 9.7 g, 47.59 mmol) and dimethylaminopyridine (DMAP, 0.4 g, 3.43 mmol) in anhydrous DCM was added slowly to the reaction medium. The resulting mixture was stirred at room temperature for 12 hours and the precipitate formed was filtered. The filtrate was washed with saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give the dibenzyl ester (**46b**) in quantitative yield. The Boc protecting group was removed with 50% aqueous TFA to give the desired product (**47**) in 95% yield.

EXAMPLE 9

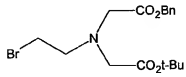
Synthesis of



[Scheme 2, **17a**] N-Alkylation of N-benzyl-N-ethanolamine with t-butyl bromoacetate was carried out as described in Example 2. Final yield of about 90% was obtained.

EXAMPLE 10

Synthesis of

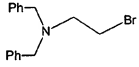


[Scheme 2, **17**] A mixture of N-benzyl-N-ethanolamine (15 mmol, 1 equiv.) and $KHCO_3$ (22.5 mmol, 1.5 equiv.) in acetonitrile (100 mL) was cooled to 0 °C and t-butyl bromoacetate (19.5 mmol, 1.3 equiv.) was added dropwise. After complete addition of the bromide, the mixture was allowed to reach room temperature and stirred for 2 hours. It was filtered and the residue was washed with acetonitrile. The solvent was evaporated from the filtrate. The crude product was taken up in 100 ml of dichloromethane and washed with water (3 X 75 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated. Further purification was performed by flash chromatography using 10% ether in hexane.

Removal of the benzyl group by catalytic hydrogenation gave the secondary amine which was alkylated with benzyl bromoacetate as described in Example 1. The alcohol was converted to bromide with triphenylphosphine and N-bromosuccinimide as described in Example 2.

EXAMPLE 11

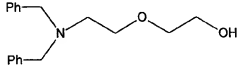
Synthesis of



N,N,N-dibenzylethanolamine was brominated with triphenylphosphine and N-bromosuccinimide as described in Example 1.

EXAMPLE 12

Synthesis of

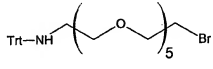


A solution of benzyl chloride (28 g, 0.25 mol) in DMF (10 mL) was added dropwise to a mixture of potassium bicarbonate (15 g, 0.15 mol) and 2-aminoethyloxyethanol (10.5 g, 0.1 mol) in 100 mL of DMF. After stirring for 16 hours at room temperature, the mixture was filtered and the filtrate was evaporated. The crude product was partitioned into water/DCM. The organic layer was washed with water, then brine and then dried over $MgSO_4$. The solvent

was evaporated and the product was isolated by flash column chromatography starting with hexane and eluting the compound with 60% ethyl acetate in hexane as a pale yellow oil (20 g, 70% yield).

EXAMPLE 13

Synthesis of



A mixture of trityl chloride (10 g, 36 mmol), tetraethyleneglycol (70 g, 360 mmol) and pyridine (4.25 g, 54 mmol) was heated at 45 °C for 16 hours. An equal volume of water was added after reaction. The mixture was centrifuged in order to accelerate the separation of phases. The aqueous phase was decanted and the sticky product was dissolved in toluene and washed thrice with water. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude intermediate product was purified by flash chromatography to give the monotrityl tetraethyleneglycol intermediate (12.7 g, 80% yield) as pale yellow oil.

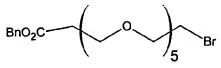
The monotrityl tetraethyleneglycol (28 mmol)) was dissolved in anhydrous dichloromethane (200 mL) and cooled to -20 °C. After addition of triethyl amine (36.75 mmol), methanesulfonyl chloride (35 mmol) was introduced dropwise. The solution was stirred at this temperature for 20 minutes then allowed to warm up to room temperature. After 3 hours, the hydrochloride salt was filtered off and the filtrate was washed twice with water then brine. Drying with $MgSO_4$ and removal of the solvent gave the pure monotrityl tetraethyleneglycol mesylate (93%).

A heterogeneous mixture of the mesylate (5 mmol), N,N-dibenzylaminoethyloxyethanol (4.2 mmol) and KOH (17 mmol) was refluxed for 20 hours. The mixture was filtered and the solvent evaporated. The residue was partitioned into water/dichloromethane. The organic layer was separated and washed with water, then brine. After drying with magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography, starting with hexane and eluting the monotrityl N,N-dibenzylaminohexaethyleneglycol with 40% ether in hexane.

The monotrityl N,N-dibenzylaminohexaethyleneglycol was hydrogenated to give the α,ω- aminoalcohol of hexaethyleneglycol. The primary amine was tritylated with trityl chloride and bromination of the primary alcohol was carried out with triphenylphosphine and NBS as described in Example 1.

EXAMPLE 14

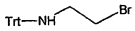
Synthesis of



Reaction of pentaethyleneglycol (50 mmol) with t-butyl propiolate (5 mmol) at room temperature for 5 hours and subsequent hydrogenation with 10% Pd-C at 45 psi gives the t-butyloxycarbonylhexaethyleneglycol. Bromination of the free primary alcohol is carried out with triphenylphosphine and NBS as described in Example 1. Removal of the t-butyl ester with HCl (1 M, 30 mL, 3 hours) and esterification of the acid with benzyl alcohol in the presence of dimethylaminopyridine gives the desired compound which could be purified by dry flash chromatography.

EXAMPLE 15

Synthesis of

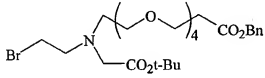


Dropwise addition of trityl chloride (15 mmol, 1 equiv.) in dichloromethane to a solution of ethanolamine (30 mmol, 2 equiv.) in DMF at 0 °C and stirring at this temperature for 6 hours gives a yellow solution. Evaporation of the solvents at below 40 °C gives a solid residue which is partitioned between ether and water. Dry the ether phase over $MgSO_4$ and evaporate the solvent to obtain the crude product which is readily purified by dry flash chromatography, eluting the pure compound with 30% ethyl acetate in hexane. The alcohol was converted to bromide with triphenylphosphine and N-bromosuccinimide as described in Example 2.

A variation of the above procedure begins with the reaction of commercially available 2-aminoethyl bromide with trityl chloride. In this procedure, there is no need for the additional step required for bromination.

EXAMPLE 16

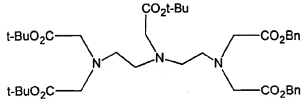
Synthesis of



[Scheme 7, **38**] Reaction of N-benzylaminoethanol (5 mmol) with t-butyl bromoacetate (5.2 mmol) gives a tertiary amine. The benzyl group is removed by catalytic hydrogenolysis with 10% Pd/C at 40 psi in methanol for 4 hours. After filtration of the catalyst, the solvent is evaporated and the resulting secondary amine is immediately alkylated with benzyl bromopentaethyleneglycolacetate in acetonitrile at reflux for 24 hours. Conversion of the alcohol with triphenylphosphine and NBS is carried out as described in Example 2.

EXAMPLE 17

Synthesis of

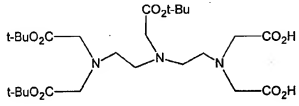


[Scheme 1, **12**] A mixture of N,N'N'-tris(t-butyloxycarbonylmethyl) ethylenediamine (4.4 g, 9.82 mmol) and 2-[Bis-(benzyloxycarbonylmethyl)amino]ethyl bromide (5.3 g, 12.76 mmol) was added to a solution of ethyldiisopropylamine (3.8 g, 29.45 mmol) in 100 ml acetonitrile. The mixture was stirred at reflux for 24 hours under nitrogen. After the reaction was complete, the solvent was evaporated and the residue was partitioned between dichloromethane (100 ml) and distilled water (100 ml). The organic layer was washed with 100 ml of water and

100 ml of brine. It was dried over magnesium sulfate and the solvent was evaporated to give about 10 g of the crude product. The product was purified by dry flash chromatography and the pure compound was eluted with 40% of diethyl ether in hexane as a pale yellow liquid (6.5 g, 90% yield).

EXAMPLE 18

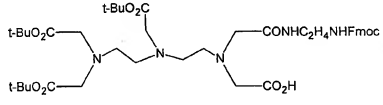
Synthesis of



[Scheme 1, **13**] A mixture of 10% palladium on carbon (0.21 g) and a solution of N,N',N'-tris(t-butyloxycarbonylmethyl)-N",N"-bis(benzyloxycarbonylmethyl)diethylenetriamine (3.3 g, 4.45 mmol) in 50 ml of methanol was hydrogenolyzed at 40 psi for 2 hours. The mixture was filtered over celite and the residue was washed with methanol. The solvent was evaporated to give an off-white powder which was shown by mass spectral analysis, HPLC and NMR to be the pure compound (2.4 g, 96% yield).

EXAMPLE 19

Synthesis of

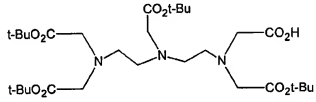


[Scheme 1, **14**] Tri-t-butyl diethylenetriaminepentaacetic acid (5.46 g, 9.72 mmol, 1 equiv.) in 20 mL DMF and dicyclohexylcarbodiimide (DCC, 2 g, 9.72 mmol, 1 equiv.) in the presence of a catalytic amount of dimethylaminopyridine (DMAP) (0.1 equiv.) were stirred at room temperature for 1 hour and mono-Fmoc ethylenediamine (2.74 g, 9.72 mmol, 1 equiv.) was

added. The resulting mixture was stirred for 6 hours at room temperature and the crude product was partitioned between dichloromethane and saline. The organic phase was washed with water and dried over $MgSO_4$. The solvent was evaporated and the DCC urea formed was precipitated with ether. After filtration, the solvent was evaporated and the product was purified by dry flash chromatography on silica gel, eluting the compound with ethyl acetate.

EXAMPLE 20

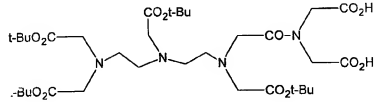
Synthesis of



[Scheme 9, 44] A mixture of N,N'N'-tris(t-butyloxycarbonylmethyl) ethylenediamine (**11**; 4.4 g, 9.82 mmol), N,N-benzyloxycarbonylmethyl-t-butyloxycarbonylmethylaminoethyl bromide (**17**;12.76 mmol) and diisopropylethylamine (3.8 g, 29.45 mmol) in 100 ml acetonitrile was heated at reflux for 18 hours. After the reaction was complete, the solvent was evaporated and the residue was partitioned between dichloromethane (100 ml) and distilled water (100 ml). The organic layer was washed with water and brine in that order. It was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by dry flash chromatography and the pure compound was eluted with 40% of diethyl ether in hexane. Hydrogenolysis of the benzyl ester was carried out as described in Example 18.

EXAMPLE 21

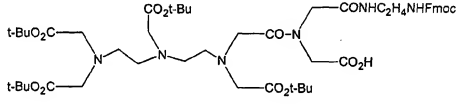
Synthesis of



[Scheme 9, **48**] Reaction of the monocarboxylic acid tetra-t-butyl diethylenetriaminepentaacetic acid (DTPA) (**44**; 1 mmol) with N,N-dibenzyloxycarbonylmethylamine (**47**; 1.2 mmol), diisopropylethylamine (1.2 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (1.1 mmol) in DMF for 5 hours at room temperature gives the dibenzyl ester conjugate which is hydrogenolyzed as described in Example 18 to give the dicarboxylic acid, **48**.

EXAMPLE 22

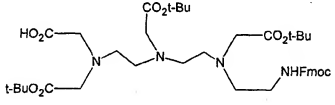
Synthesis of



[Scheme 9, **49**] Conjugation of mono-Fmoc ethylenediamine to the dicarboxylic acid of Example 21 was carried out as described in Example 19.

EXAMPLE 23

Synthesis of

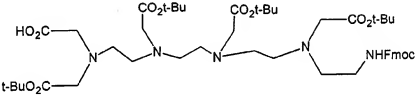


Dissolve benzylethylenediamine (**9**; 10.3 mmol, 1 equiv.) in dry dichloromethane (10 mL) and cool the solution to -5 °C. Add ethyl trifluoroacetate (10.3 mmol, 1 equiv.) dropwise while maintaining the temperature below 0 °C. After addition, stir at this temperature for 2 hours and allow the reaction mixture to warm up to room temperature and stir for additional 2 hours. Evaporate the solvent and any unreacted trifluoroacetate and purify the crude product by dry flash chromatography if desired. Dissolve the crude product in anhydrous DMF (20 mL) and cool the

solution to 0 °C. Add sodium hydride (20.6 mmol, 2 equiv.) and stir the mixture for 10 minutes before adding t-butyl bromoacetate (20.6 mmol, 2 equiv.) dropwise. Allow the mixture to warm up to room temperature and stir for 12 hours. Remove the solvent *in vacuo* and partition the residue between dichloromethane and water. Wash the organic layer with water and dry it over $MgSO_4$. After evaporating the solvent, redissolve the residue in acetonitrile and react it with N,N-benzyloxycarbonylmethyl-t-butyloxycarbonylmethylaminoethyl bromide (17; 22 mmol) as described in Example 17. Deprotect the trifluoroacetyl group with hydrazine in t-butanol at 0 °C and react the ensuing secondary amine with N-tritylethyl bromide as described in Example 17. Catalytic hydrogenation of the product with 10% Pd-C catalyst and subsequent protection of the free amine with Fmoc-succinimide yields the desired compound which can be purified by flash chromatography.

EXAMPLE 24

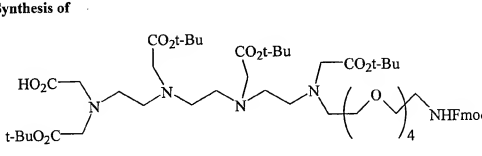
Synthesis of



The product is prepared as described in Example 23 starting with benzyl diethylenetriamine.

EXAMPLE 25

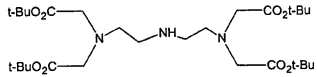
Synthesis of



[Scheme 6, **35**] Add triglycine (**31**) to DMF and diisopropylethylamine. Slowly add benzoyl chloride at 0°C. After addition is complete, gently evaporate the solvent and purify the intermediate by dry flash chromatography. Redissolve the benzylamide in DMF and transfer it to a pressure bottle. Activate the free carboxyl group with HBTU for 30 minutes and cool the mixture to 0°C. Charge the pressure bottle with ammonia and seal the bottle. Stir the mixture for 4 hours, then cool it to 0°C before opening the bottle. Purify the primary amide (**32**) by flash chromatography and reduce the tetraamide with lithium aluminum hydride. Selectively protect the ensuing primary amine with ethyl trifluoroacetate to give the intermediate orthogonally-protected secondary amine (**33**). Add t-butyl bromoacetate to a mixture of **33** and potassium carbonate in acetonitrile and stir the mixture at room temperature for 16 hours. Evaporate the solvent and purify the resulting product. Selectively remove the benzyl protecting group by catalytic hydrogenolysis with 10% Pd-C and alkylate the secondary amine with N-tritylaminotetraethyleneglycolethyl bromide to give **34**. Remove the trifluoroacetyl group as described in Example 8 and alkylate the secondary amine with benzyl bromoacetate. Catalytic hydrogenolysis at 50 psi with 10% Pd-C in methanol removes both N-trityl and benzyl ester to give the unprotected amino acid. Reaction of the free amine with Fmoc-succinimide yields compound **35**.

EXAMPLE 26

Synthesis of



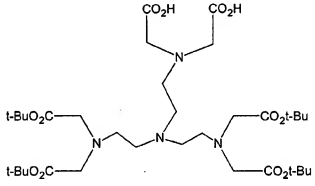
[Scheme 5, **28**] A mixture of 2-[Bis-(t-butyloxycarbonylmethyl)amino]ethyl bromide (**27**; 6.0 g, 17.05 mmol), diisopropylethylamine (4.4 g, 34.1 mmol) and benzylamine (0.9 g, 8.41 mmol) in 100 ml of anhydrous acetonitrile was refluxed for 16 hours under argon. After reaction, the solvent was evaporated en vacuo and the residue was partitioned between dichloromethane (100 ml) and water (100 ml). The two layers formed were separated and the organic phase was washed with water (100 ml) and brine (100 ml) in that order. The dichloromethane layer was dried over magnesium sulfate and the solvent was removed en vacuo to give 7 g of the crude

product. The crude product was dissolved in hexane and purified by dry flash chromatography with 20% diethyl ether in hexane to give 4.2 g (76%) of the pure compound as a pale yellow liquid.

A mixture of 10% palladium on carbon (0.4 g) and a solution of the purified intermediate N'-benzyl-N,N''-tetrakis(t-butyloxycarbonylmethyl)-diethylenetriamine (6.16 mmol) in 100 ml of methanol was hydrogenolyzed at 50 psi for 2 hours. The mixture was filtered over celite and the residue was washed with methanol (50 ml). The solvent was evaporated to give the pure product (95%) as a viscous oil.

EXAMPLE 27

Synthesis of

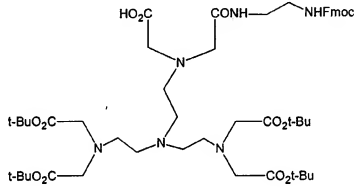


[Scheme 5, **29**] A mixture of 2-[Bis-(benzyloxycarbonylmethyl)amino]ethyl bromide (**11b**; 17.05 mmol), diisopropylethylamine (34.1 mmol) and N,N''-tetrakis(t-butyloxycarbonylmethyl) diethylenetriamine (**28**;15 mmol) in 200 ml of anhydrous acetonitrile was refluxed for 16 hours under argon. After reaction, the solvent was evaporated *in vacuo* and the residue was partitioned between dichloromethane (200 ml) and water (200 ml). The two layers formed were separated and the organic phase was washed with water (200 ml) and brine (200 ml) in that order. The dichloromethane layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give a viscous liquid residue which was dissolved in hexane and purified by dry flash chromatography with 20% diethyl ether in hexane to give the pure compound (65%) as a pale yellow liquid. The benzylester was removed by catalytic

hydrogenation in methanol (200 mL) with 10% palladium on carbon (0.4 g) at 50 psi for 1 hour. The mixture was filtered over celite and the residue was washed with methanol (2 x 50 ml). The solvent was evaporated to give the pure product .

EXAMPLE 28

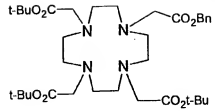
Synthesis of



[Scheme 5, **30**] Activation of N'- [Bis-(carboxylmethyl)amino]ethyl-N,N''-tetrakis(t-butyloxycarbonylmethyl) diethylenetriamine (**29**; 5 mmol, 1 equiv.) with HBTU (5.1 mmol) and diisopropylethylamine (10 mmol) in 40 mL DMF for 1 hour and subsequent reaction of the intermediate with mono-Fmoc ethylenediamine (5 mmol, 1 equiv) at room temperature for 6 hours gives a heterogeneous mixture. Partition the mixture between dichloromethane and saline and wash the organic phase with water. Dry the dichloromethane solution over $MgSO_4$ and evaporate the solvent to give the crude product which is readily purified by dry flash chromatography, starting with 10% ethyl acetate in hexane and eluting the pure compound with ethyl acetate.

EXAMPLE 29

Synthesis of

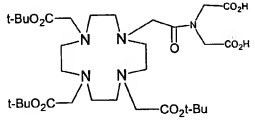


[Scheme 11, **55**] Cyclen [1,4,7,10-tetraazacyclododecane] (**53**; 2.9 g, 16.8 mmol) was dissolved in chloroform (50 mL) and a solution of benzyl bromoacetate (1.92, 8.4 mmol) in acetonitrile was added dropwise. The mixture was stirred for 1.5 hours and the solvent was evaporated to give an oil which was purified by flash chromatography to give monobenzyloxycarbonylmethylcyclen (**54**; 2 g, 75%)

t-Butyl bromoacetate (3.5 g, 18 mmol) in 5 mL acetonitrile was added dropwise to a mixture of cyclen mono-benzyl ester (1.41 g, 4.4 mmol) and K_2CO_3 (2.5 g, 18 mmol) in acetonitrile (25 mL). The resulting mixture was stirred at room temperature for 2 hours and the salt was filtered. The filtrate was evaporated and the residue was purified by flash chromatography to give the N-benzyloxycarbonylmethyl-N',N''N'''-tris(t-butyloxycarbonylmethyl)cyclen (**55**; 3 g).

EXAMPLE 30

Synthesis of

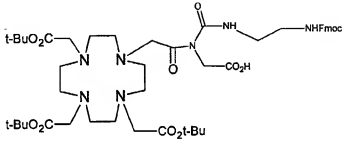


[Scheme 11, **57**] The benzyl ester of benzyloxycarbonylmethyl-N',N''N'''-tris(t-butyloxycarbonylmethyl)cyclen (**55**, 3 g) was removed by catalytic hydrogenation using 10% Pd-

C as described in Example 18. React the cyclen monoacetic acid (**56**) with N,N-bis(benzyloxycarbonylmethyl)amine (**47**) as described in Example 19 and hydrogenolyze the dibenzyl ester as described in Example 18 to give compound **57**.

EXAMPLE 31

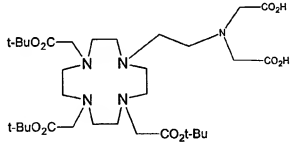
Synthesis of



[Scheme 11, **58**] Reaction of mono-Fmoc ethylenediamine with the dicarboxylic acid **57** from Example 30 follows the same procedure described in Example 19.

EXAMPLE 32

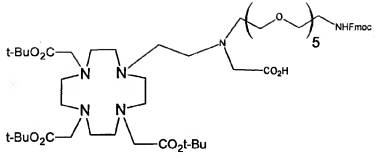
Synthesis of



[Scheme 12, **60**] Reaction of N',N'',N'''-tris(t-butyloxycarbonylmethyl)cyclen (**59**; 1 mmol) with bis(benzyloxycarbonylmethyl)aminoethyl bromide (**11b**; 1.1 mmol) as described in Example 17 gives the dibenzyl ester which was hydrogenolyzed as described in Example 18.

EXAMPLE 33

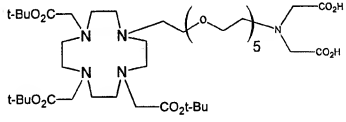
Synthesis of



[Scheme 12, **61**] Reaction of N-trityl-pentaethyleneglycolethyl bromide (2.1 mmol) with N,N-benzylethanolamine (2.0 mmol) in acetonitrile at room temperature in the presence of K_2CO_3 (2 mmol) gives N'-trityl-pentaethyleneglycolethyl-N-benzylethanol and the alcohol is brominated with triphenylphosphine and NBS as described in Example 1. Conjugation of the bromide to N'',N''',N''''-tris(t-butyloxycarbonylmethyl)cyclen [**59**] and subsequent removal of the N-benzyl group gives the secondary alkylamine. Reaction of this amine with benzyl bromoacetate and removal of the benzyl group yields the desired product [**61**].

EXAMPLE 34

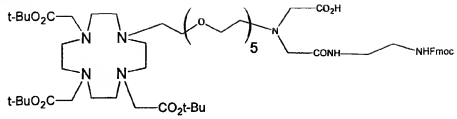
Synthesis of



The reaction of N'',N''',N''''-tris(t-butyloxycarbonylmethyl)cyclen (**59**) with N,N-bis(benzyloxycarbonylmethyl)-N-pentaethyleneglycolethyl bromide as described in Example 17 gives the dibenzyl ester which was hydrogenolyzed as described in Example 18 to give the dicarboxylic acid.

EXAMPLE 35

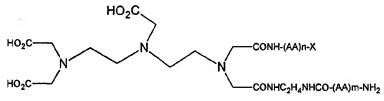
Synthesis of



The procedure for the conjugation of the mono-Fmoc ethylenediamine with the dicarboxylic acid of Example 34 is the same as in Example 22.

EXAMPLE 36

Synthesis of bis-peptide-chelate conjugate, method A



X = COOH; (AA)m = Octreotate for somatostatin receptor positive tumors

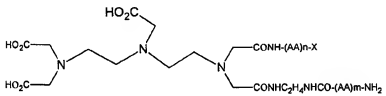
(AA)n = Bombesin (7-14) for bombesin receptor positive tumors

[Scheme 13, **64**] The DTPA-Octreotate conjugate was prepared by solid phase synthesis using pre-loaded fluorenemethoxycarbonyl-threonine (Fmoc-Thr) Wang resin on 0.025 mmol scale. Commercially available automated peptide synthesizer from Applied Biosystems (Model 432A SYNERGY Peptide Synthesizer) was used. Cartridges containing Fmoc-protected amino acids were used in the solid phase synthesis. Cysteines were protected with acetamidomethyl group. Coupling reaction was carried out with 0.075 mmol of the protected amino acid and 2-(1H-benzotriazole-1yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)/N-hydroxybenzotriazole (HOBt) in the presence of diisopropylethylamine. The amino acids and tri-t-butyl DTPA cartridges were placed on the peptide synthesizer and the product was synthesized from the C-terminal to the N-terminal position.

After the synthesis of the first peptide and conjugation of the chelator was complete, the free acid from tri-t-butyl DTPA was activated on solid support with HBTU/HOB (1.5 equiv.) for 30 minutes and mono-Fmoc ethylenediamine (3 equiv.) was added in the presence of diisopropylethylamine (3 equiv.). The mixture was shaken for 2 hours and the resin was washed with DMF and THF. After drying the resin, it was placed on the resin cartridge and the second peptide (bombesin (7-14) was synthesized automatically. At the end of the reaction, the disulfide bond was formed between the two Cysteines of the octreotate peptide with thallium trifluoroacetate. The product was cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. Note that the t-butyl esters of tri-t-butyl DTPA were also cleaved to give the free tetra-carboxylic acid. The DTPA-bispeptide conjugate was precipitated with t-butyl methyl ether and lyophilized with water : acetonitrile (2/3) mixture. The crude product was purified by HPLC to give the desired product as shown by mass spectral analysis.

EXAMPLE 37

Synthesis of bis-peptide-chelator conjugate, method B



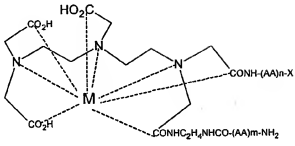
X = COOH; (AA)m = Octreotate for somatostatin receptor positive tumors

(AA)n = Bombesin (7-14) for bombesin receptor positive tumors

[Scheme 14, **64**] In this method, the mono-Fmoc ethylene diamine tri-t-butyl DTPA (compound of Example 19) was used in place of tri-t-butyl DTPA. This procedure permitted the automatic synthesis of the bis-peptide without interruption. The disulfide bond was formed and the bis-peptide on solid support was cleaved as described in the preceding example.

EXAMPLE 38

Synthesis of bis-peptide-chelate conjugate



X = COOH; (AA)m = Octreotate for somatostatin receptor positive tumors

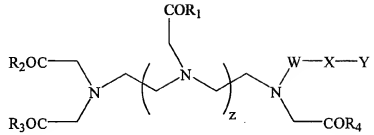
(AA)n = Bombesin (7-14) for bombesin receptor positive tumors

M = indium-115 (^{115}In)

[Scheme 14, **65**] The ^{115}In -DTPA-bispeptide complex was prepared by reacting the DTPA-bispeptide (50 mmol) with $^{115}InCl_3$ (90 mmol) in 170 μL of aqueous HCl (5 nM) at room temperature for 30 minutes. The solution was neutralized lyophilized and purified by HPLC to obtain the desired compound.

WHAT IS CLAIMED IS:

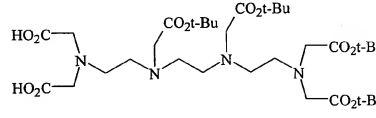
1. A compound of formula

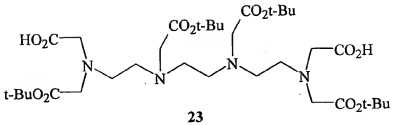


1

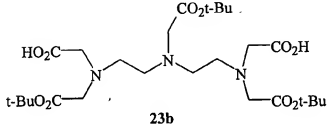
wherein R_1 to R_4 may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X-Y; W is selected from the group consisting of alkyl, aryl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, polyhydroxyalkyl, and polyhydroxyaryl; X is selected from the group consisting of -NH, -CONH-, $-CH_2NH$-, $-CH_2NR_3$-, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y is selected from the group consisting of H, CH_2COOH, peptide, biomolecule, an Fmoc protected amine or a Boc protected amine; b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_3 is as defined for R_1; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and z varies from 1-10.

2. The compound of claim 1 wherein said compound is selected from the group consisting of



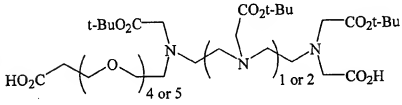


23

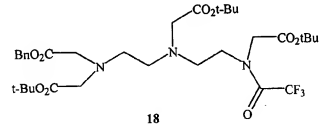


23b

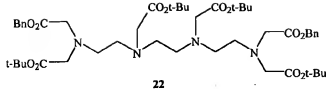
, and



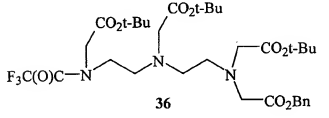
3. The compound of claim 1 wherein said compound is selected from the group consisting of



18

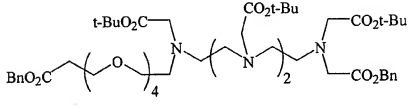


22



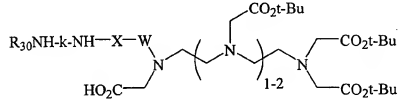
36

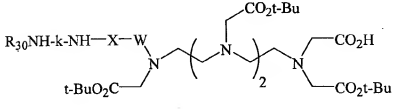
, and



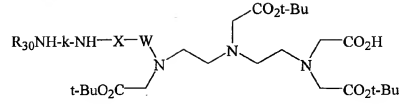
39b

4. The compound of claim 1 wherein said compound is selected from the group consisting of





, and

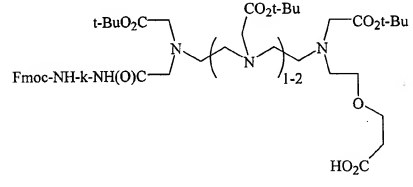


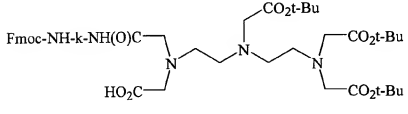
5. The compound of claim 4 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

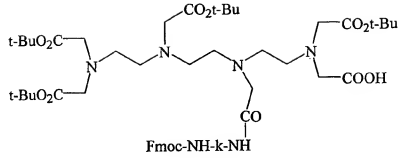
6. The compound of claim 4 wherein NH-k-NH is an orthogonally protected diamine.

7. The compound of claim 4 wherein R_{30} is Fmoc.

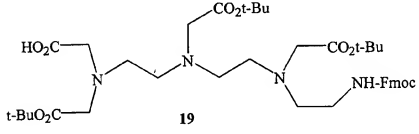
8. The compound of claim 1 wherein said compound is selected from the group consisting of:





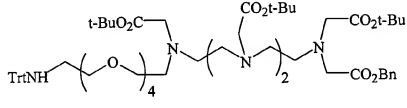


, and



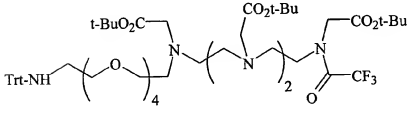
19

9. The compound of claim 1 wherein said compound is selected from the group consisting of:



39a

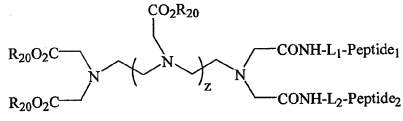
and



34

10. The compound of claim 1 wherein said compound is a bis-peptide.

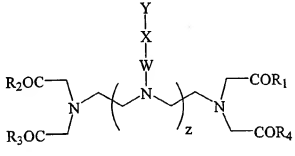
11. The compound of claim 10 wherein said compound is



5

wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of $-(CH_2)_t-NHC(O)-$ or $-CH_2-(CH_2-O-CH_2)_u-NHC(O)-$; t varies from 1 to 10; u varies from 1 to 50; and z varies from 1 to 10.

12. A compound of the formula

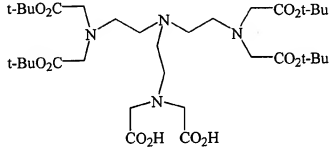


1a

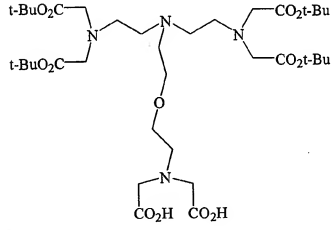
wherein R_1 to R_4 may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X-Y; W is selected from the group consisting of alkyl, aryl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, polyhydroxyalkyl, and polyhydroxyaryl; X is selected from the group consisting of -NH, -CONH-, $-CH_2NH-$, $-CH_2NR_5-$, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y is selected from the group consisting of H, CH_2COOH, peptide, biomolecule, an Fmoc protected amine or a

Boc protected amine; b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_5 is as defined for R_1; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and z varies from 1-10.

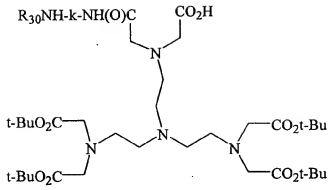
13. The compound of claim 12 wherein said compound is selected from the group consisting of:



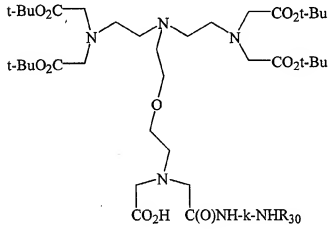
and **29**



14. The compound of claim 12 wherein said compound is selected from the group consisting of:



and



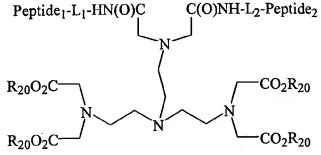
15. The compound of claim 14 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

16. The compound of claim 14 wherein NH-k-NH is an orthogonally protected diamine.

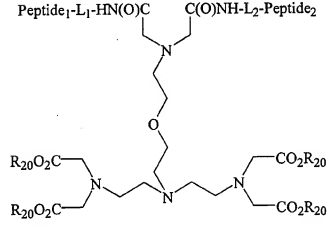
17. The compound of claim 14 wherein R_{30} is Fmoc.

18. The compound of claim 12 wherein said compound is a bis-peptide.

19. The compound of claim 12 wherein said compound is

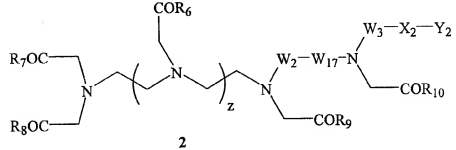


or



wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of -$(CH_2)_t$-NHC(O)- or -CH_2-$(CH_2$-O-$CH_2)_u$-NHC(O)-; t varies from 1 to 10; and u varies from 1 to 50.

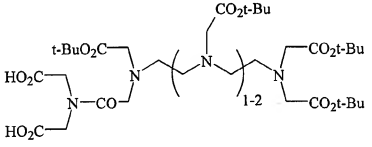
20. A compound of formula



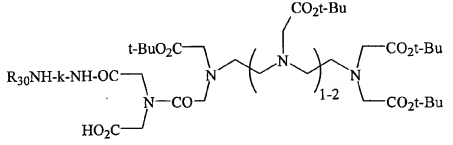
2

wherein one of R_6 to R_{10} is H; R_6 to R_{10} may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X_2-Y_2; W_2 is selected from the group consisting of alkyl, aryl, $-CH_2(CH_2-O-CH_2)_5CH-R_a$, polyhydroxyalkyl, and polyhydroxyaryl; X_2 is selected from the group consisting of -NH, -CONH-, $-CH_2NH-$, $-CH_2NR_5-$, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y_2 is selected from alkyl amines, aryl amines, polyhydroxyalkyl amines, polyalkoxyalkyl amines, bioactive molecules, an Fmoc protected amine or a Boc protected amine; W_{17} is C=O, CH_2, or OC_2H_4; b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_5 is as defined for R_6; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and z varies from 1-10.

21. The compound of claim 20 wherein said compound is



22. The compound of claim 20 wherein said compound is



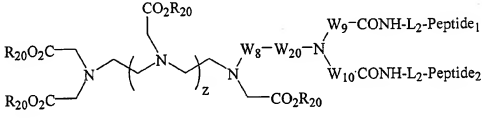
23. The compound of claim 22 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

24. The compound of claim 22 wherein NH-k-NH is an orthogonally protected diamine.

25. The compound of claim 22 wherein R_{30} is Fmoc.

26. The compound of claim 20 wherein said compound is a bis-peptide.

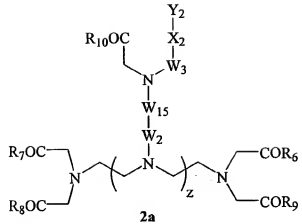
27. The compound of claim 26 wherein said compound is



6

wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of $-(CH_2)_t$-NHC(O)- or $-CH_2-(CH_2-O-CH_2)_u$-NHC(O)-; t varies from 1 to 10; u varies from 1 to 50; and z varies from 1 to 10.

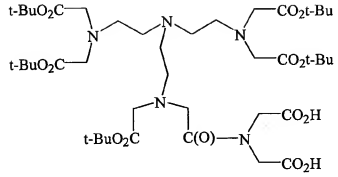
28. A compound of formula



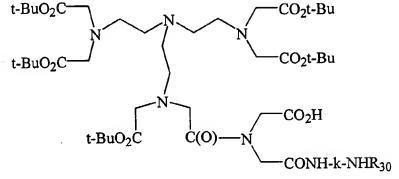
2a

wherein one of R_6 to R_{10} is H; R_6 to R_{10} may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, -CH_2(CH_2-O-CH_2)$_b$-CH_2-R_a, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X_2-Y_2; W_2 is selected from the group consisting of alkyl, aryl, -CH_2(CH_2-O-CH_2)$_b$-CH_2-R_a, polyhydroxyalkyl, and polyhydroxyaryl; X_2 is selected from the group consisting of -NH, -CONH-, -CH_2NH-, -CH_2NR_3-, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y_2 is selected from alkyl amines, aryl amines, polyhydroxyalkyl amines, polyalkoxyalkyl amines, bioactive molecules, an Fmoc protected amine or a Boc protected amine; W_{17} is C=O, CH_2, or OC_2H_4; b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_3 is as defined for R_6; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, -CH_2(CH_2-O-CH_2)$_b$-CH_2-R_a, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and z varies from 1-10.

29. The compound of claim 28 wherein said compound is



30. The compound of claim 28 wherein said compound is



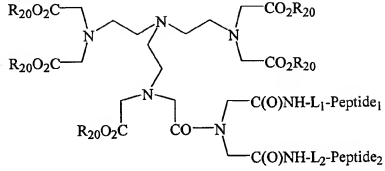
31. The compound of claim 30 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

32. The compound of claim 30 wherein NH-k-NH is an orthogonally protected diamine.

33. The compound of claim 30 wherein R_{30} is Fmoc.

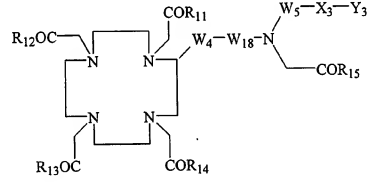
34. The compound of claim 28 wherein said compound is a bis-peptide.

35. The compound of claim 28 wherein said compound is



wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of $-(CH_2)_t-NHC(O)-$ or $-CH_2-(CH_2-O-CH_2)_u-NHC(O)-$; t varies from 1 to 10; and u varies from 1 to 50.

36. A compound of formula

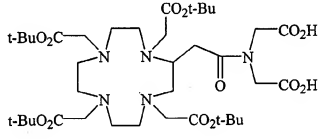


3

wherein one of R_{11} to R_{15} is H; R_{11} to R_{15} may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X_3-Y_3; W_4 and W_5 are selected from the group consisting of alkyl, aryl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, polyhydroxyalkyl, and polyhydroxyaryl; X_3 is selected from the group consisting of -NH, -CONH-, $-CH_2NH-$, $-CH_2NR_5-$, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y_3 is selected from alkyl amines, aryl amines, polyhydroxyalkyl amines, polyalkoxyalkyl

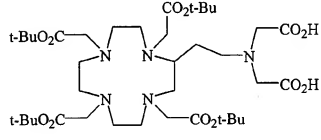
amines, bioactive molecules, an Fmoc protected amine or a Boc protected amine; W_{18} is C=O, CH_2, or OC_2H_4; b varies from 1-100; R_x may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_5 is as defined for R_{11}; R_{30} is an amine protecting group; and k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_x$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y.

37. The compound of claim 36 wherein said compound is selected from the group consisting of:

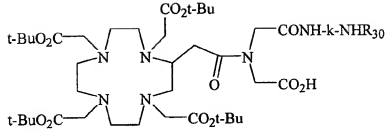


51

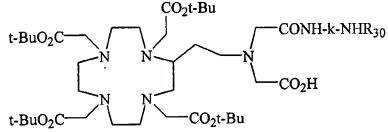
and



38. The compound of claim 36 wherein said compound is selected from the group consisting of:



and



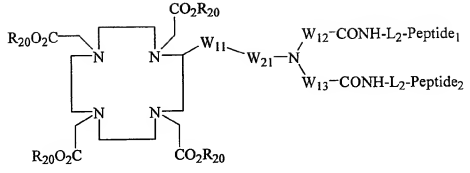
39. The compound of claim 38 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

40. The compound of claim 38 wherein NH-k-NH is an orthogonally protected diamine.

41. The compound of claim 38 wherein R_{30} is Fmoc.

42. The compound of claim 36 wherein said compound is a bis-peptide.

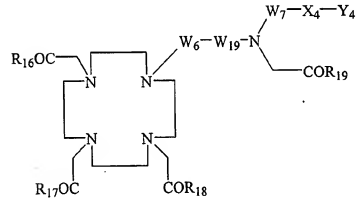
43. The compound of claim 40 wherein said compound is



7

wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of -$(CH_2)_t$-NHC(O)- or -CH_2-$(CH_2$-O-$CH_2)_u$-NHC(O)-; t varies from 1 to 10; and u varies from 1 to 50.

44. A compound of formula

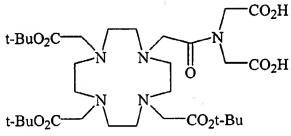


4

wherein one of R_{16} to R_{19} is H; R_{16} to R_{19} may be the same or different and are selected from the group consisting of alkyl, aryl, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, -$CH_2(CH_2$-O-$CH_2)_b$-CH_2-R_a, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X_4-Y_4; W_6 and W_7 are selected from the group consisting of alkyl, aryl, -$CH_2(CH_2$-O-$CH_2)_b$-CH_2-R_a, polyhydroxyalkyl, and polyhydroxyaryl; X_4 is selected from the group consisting of -NH, -CONH-, -CH_2NH-, -CH_2NR_3-, -COO-, -O-, -C(O)-, -S-, -NHCO-, and -NHC(S)-; Y_4 is selected from alkyl amines, aryl amines, polyhydroxyalkyl amines, polyalkoxyalkyl

amines, bioactive molecules, an Fmoc protected amine or a Boc protected amine; W_{19} is C=O, CH_2, or OC_2H_4; b varies from 1-100; R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_5 is as defined for R_{16}; R_{30} is an amine protecting group; and k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2\text{-}O\text{-}CH_2)_b\text{-}CH_2\text{-}R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y.

45. The compound of claim 44 wherein said compound is selected from the group consisting of:



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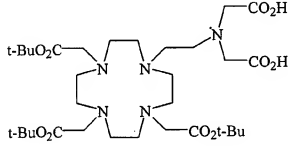
and



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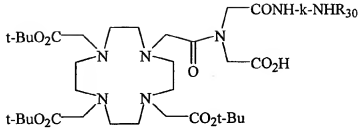
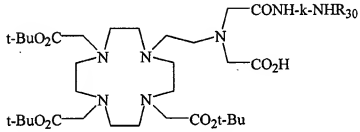
46. The compound of claim 44 wherein said compound is selected from the group consisting of:



and



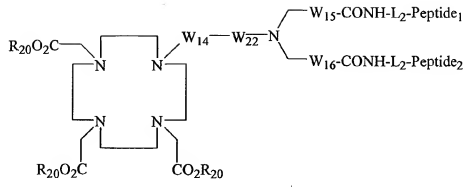
47. The compound of claim 46 wherein NH-k-NH is selected from the group consisting of ethylenediamine; bis(2-aminoethyl)-ether; O-bis(aminoethyl)ethylene glycol; O-bis(aminoethyl)tetraethylene glycol; O-bis(aminoethyl)hexaethylene glycol; 1,4-bis(aminomethyl)benzene; 1,3-bis(aminomethyl)benzene; 1,4-diaminobutane; 1,2-diaminocyclohexane; 4,4'-diaminodicyclohexylmethane; N-1,3-diamino-2-propanol; homopiperazine; piperazine; histidine; and lysine.

48. The compound of claim 46 wherein NH-k-NH is an orthogonally protected diamine.

49. The compound of claim 46 wherein R_{30} is Fmoc.

50. The compound of claim 44 wherein said compound is a bis-peptide.

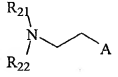
51. The compound of claim 50 wherein said compound is



8

wherein each R_{20} is H, t-butyl or benzyl; L_1 and L_2 may be the same or different and may be a single bond or are taken from the group consisting of $-(CH_2)_t$-NHC(O)- or $-CH_2-(CH_2-O-CH_2)_u$-NHC(O)-; t varies from 1 to 10; and u varies from 1 to 50.

52. A compound of formula



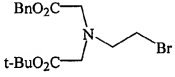
wherein R_{21} and R_{22} can be the same or different and are selected from the group consisting of alkyl, alkyl ester, aryl, aryl ester, heterocarbocyclic, NH-k-NHR_{30}, CH_2CO_2H, hydroxyl, amino, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2$-Ra, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, and X-Y; X is selected from the group consisting of -NH, -CONH-, $-CH_2NH-$, $-CH_2NR_5-$, -COO-, -O-, -S-, -NHCO-, and -NHC(S)-; Y is selected from the group consisting of H, CH_2COOH, peptide, biomolecule, an Fmoc protected amine or a Boc protected amine; b varies from 1-100, R_a may be H, OH, -O-, alkyloxy, aryl, alkyl or single bond; R_5 i s as defined for R_1; R_{30} is an amine protecting group; k is alkyl, aryl, heterocarbocyclic, CH_2CO_2H, C1-C10 alkoxyl, C1-C10 aryloxyl, C1-C10 polyalkoxyalkyl, $-CH_2(CH_2-O-CH_2)_b-CH_2-R_a$, C1-C20 polyhydroxyalkyl, C1-C10 polyhydroxyaryl, carbocyclic, heterocyclic, or X-Y; and wherein A is a halide.

53. The compound of claim 52 wherein R_{21} is benzyl.

54. The compound of claim 52 wherein R_{22} is t-butyl.

55. The compound of claim 52 wherein A is bromo.

56. The compound of claim 52 wherein said compound is



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